

CLAIMS

1. A method of [^{11}C]-radiolabelling a phenothiazine compound or a phenothiazine-like compound, wherein:

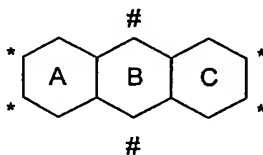
5 said compound has a polycyclic core of three six-membered rings fused together in a linear fashion and denoted the A-ring, B-ring, and C-ring, where the B-ring is the "middle" ring;

 said polycyclic core is partially-aromatic or fully-aromatic;

10 said polycyclic core has 14 ring atoms, including exactly 1 or exactly 2 ring heteroatom(s), each of which is independently selected from N, O, and S;

 the remainder of said ring atoms being C;

15 said exactly 1 or exactly 2 ring heteroatom(s) form part of the B-ring, but not part of the A-ring or C-ring, and so are located at one or both of the "central" positions denoted by a hash-mark (#) in the following depiction of the polycyclic core:



 said compound has a pendant group covalently attached to a ring atom of said polycyclic core;

20 said pendant group is independently:

 a primary amino group;

 a cationic primary imino group;

 a secondary amino group;

 a cationic secondary imino group;

 a primary imino group; or

25 a secondary imino group;

 said method comprising the step of:

 reacting said phenothiazine compound or a phenothiazine-like compound with [^{11}C]methyl trifluoromethanesulfonate ($\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$);

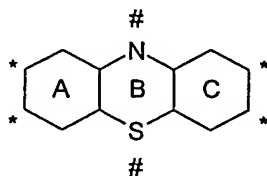
30 thereby converting said pendant group to a corresponding [^{11}C]methyl-labelled pendant group, respectively;

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a [^{11}C]methyl-labelled secondary amino group;
a [^{11}C]methyl-labelled cationic secondary imino group;
a [^{11}C]methyl-labelled tertiary amino group;
a [^{11}C]methyl-labelled cationic tertiary imino group;
5 a [^{11}C]methyl-labelled secondary imino group; or
a [^{11}C]methyl-labelled cationic tertiary imino group;
to give a [^{11}C]-radiolabelled phenothiazine or phenothiazine-like
compound.

10 2. A method according to claim 1, wherein said polycyclic core has 14 ring atoms,
including exactly 2 ring heteroatoms, each of which is independently selected from
N, O, and S.

15 3. A method according to claim 1, wherein said polycyclic core has 14 ring atoms,
including exactly 2 ring heteroatoms: N and S:



4. A method according to any one of claims 1 to 3, wherein said polycyclic core is
fully-aromatic.

20 5. A method according to any one of claims 1 to 4, wherein said pendant group is
independently attached to a ring carbon atom of said polycyclic core.

25 6. A method according to any one of claims 1 to 4, wherein said pendant group is
independently attached to a ring carbon atom of said A-ring or C-ring, but not of
said B-ring.

30 7. A method according to any one of claims 1 to 4, wherein said pendant group is
independently attached at one of the "distal" positions of said A-ring or C-ring,
which positions are denoted by asterisks (*).

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8. A method according to any one of claims 1 to 7, wherein said pendant group is independently:

a secondary amino group or
a cationic secondary imino group;

5 and said corresponding [^{11}C]methyl-labelled pendant group, respectively, is:

a [^{11}C]methyl-labelled tertiary amino group; or
a [^{11}C]methyl-labelled cationic tertiary imino group.

9. A method according to any one of claims 1 to 7, wherein said pendant group is independently selected from:

$-\text{NH}_2$, $-\text{NHR}$, $=\text{N}^{(+)}\text{H}_2$, $=\text{N}^{(+)}\text{HR}$, $=\text{NH}$, and $=\text{NR}$;

wherein R is independently selected from C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} cycloalkyl, and C_{1-6} cycloalkenyl, and is optionally substituted with one or more groups selected from halo (e.g., fluoro, chloro, bromo, iodo), hydroxy, and

15 C_{1-4} alkoxy;

and said corresponding [^{11}C]methyl-labelled pendant group, respectively, is:

$-\text{NH}-(^{11}\text{CH}_3)$, $-\text{NR}-(^{11}\text{CH}_3)$, $=\text{N}^{(+)}\text{H}-(^{11}\text{CH}_3)$, $=\text{N}^{(+)}\text{R}-(^{11}\text{CH}_3)$, or $=\text{N}-(^{11}\text{CH}_3)$.

10. A method according to any one of claims 1 to 7, wherein said pendant group is independently selected from: $-\text{NHR}$ and $=\text{N}^{(+)}\text{HR}$;

wherein R is independently selected from C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} cycloalkyl, and C_{1-6} cycloalkenyl, and is optionally substituted with one or more groups selected from halo (e.g., fluoro, chloro, bromo, iodo), hydroxy, and

25 C_{1-4} alkoxy;

and said corresponding [^{11}C]methyl-labelled pendant group, respectively, is: $-\text{NR}-(^{11}\text{CH}_3)$ or $=\text{N}^{(+)}\text{R}-(^{11}\text{CH}_3)$.

11. A method according to claim 9 or 10, wherein R is independently C_{1-4} alkyl.

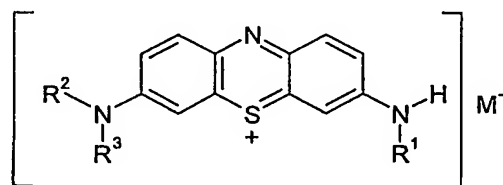
12. A method according to claim 9 or 10, wherein R is independently $-\text{Me}$ or $-\text{Et}$.

13. A method according to claim 9 or 10, wherein R is independently $-\text{Me}$.

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14. A method according any one of claims 1 to 13, wherein said compound has, in addition to said pendant group, one or more additional substituents selected from:
amino (-NH₂), methylamino (-NHMe), dimethylamino (-NMe₂), ethylamino (-NH₂Et), diethylamino (-NEt₂), imino (=NH), methylimino (=NMe), ethylimino (=NEt), methyl (-Me), ethyl (-Et), fluoro (-F), chloro (-Cl), bromo (-Br), iodo (-I), oxo (=O), hydroxy (-OH), carboxy (-COOH), and protonated and deprotonated forms thereof.

15. A method according to claim 1, wherein the phenothiazine or phenothiazine-like compound is a compound of the following formula:



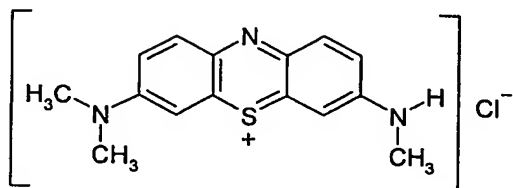
wherein:

each of R¹, R², and R³ is independently -H, C₁₋₆alkyl, C₁₋₆alkenyl, C₁₋₆alkynyl, C₁₋₆cycloalkyl, and C₁₋₆cycloalkenyl, and is optionally substituted with one or more groups selected from halo (e.g., fluoro, chloro, bromo, iodo), hydroxy, and C₁₋₄alkoxy; and

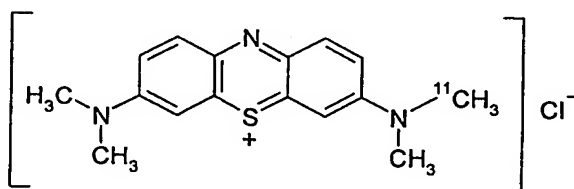
M⁻ is an anion.

16. A method according to claim 15, wherein -NHR¹ is independently -NHMe.
17. A method according to claim 15 or 16, wherein -NR²R³ is independently -NH₂.
18. A method according to claim 15 or 16, wherein -NR²R³ is independently -NHMe.
19. A method according to claim 15 or 16, wherein -NR²R³ is independently -NMe₂.
20. A method according to any one of claims 15 to 19, wherein M⁻ is independently a halide ion.
21. A method according to any one of claims 15 to 19, wherein M⁻ is independently Cl⁻.

22. A method according to claim 1, wherein the phenothiazine or phenothiazine-like compound is Azure B:



and said [^{11}C]-radiolabelled phenothiazine or phenothiazine-like compound is [N-methyl- ^{11}C]methylene blue:



23. A method according to any one of claims 1 to 22, wherein said reaction is performed in the presence of a Bronsted base.
24. A method according to any one of claims 1 to 22, wherein said reaction is performed in the presence of an alkali metal carbonate or bicarbonate.
25. A method according to any one of claims 1 to 22, wherein said reaction is performed in the presence of potassium carbonate (K_2CO_3).
26. A method according to any one of claims 1 to 25, wherein said reaction is carried out in aqueous media.
27. A method according to any one of claims 1 to 25, wherein said reaction is carried out by introducing said [^{11}C]methyl trifluoromethanesulfonate into an aqueous solution or suspension of said phenothiazine or phenothiazine-like compound, to form a reaction mixture.
28. A method according to claim 27, wherein said aqueous solution or suspension further comprises a Bronsted base.

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29. A method according to claim 27, wherein said aqueous solution or suspension further comprises an alkali metal carbonate or bicarbonate.
30. A method according to claim 27, wherein said aqueous solution or suspension further comprises potassium carbonate (K_2CO_3).
31. A method according to any one of claims 27 to 30, wherein said reaction mixture is mixed for a mixing time of 1-30 minutes.
32. A method according to any one of claims 27 to 30, wherein said reaction mixture is mixed for a mixing time of 1-10 minutes.
33. A method according to any one of claims 27 to 32, wherein said reaction is carried out at 20°C-25°C.
34. A method according to any one of claims 27 to 32, wherein said reaction is carried out under an inert atmosphere.
35. A method according to any one of claims 27 to 32, wherein said reaction is carried out under argon.
36. A method according to any one of claims 1 to 35, further comprising the subsequent step of:
purifying said [^{11}C]-radiolabelled phenothiazine or phenothiazine-like compound.
37. A method according to any one of claims 1 to 35, further comprising the subsequent step of:
purifying said [^{11}C]-radiolabelled phenothiazine or phenothiazine-like compound using ion exchange methods.
38. A method according to any one of claims 1 to 35, further comprising the subsequent step of:
purifying said [^{11}C]-radiolabelled phenothiazine or phenothiazine-like compound using cation exchange methods.

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39. A method according to any one of claims 1 to 38, wherein the reaction and optional purification is performed in less than 60 minutes.
40. A method according to any one of claims 1 to 38, wherein the reaction and optional purification is performed in less than 45 minutes.
41. A method according to any one of claims 1 to 38, wherein the reaction and optional purification is performed in less than 40 minutes.
42. A method according to any one of claims 1 to 41, which provides a radiochemical purity greater than 90%.
43. A method according to any one of claims 1 to 42, which provides a radiochemical yield of at least 2%.
44. A method according to any one of claims 1 to 43, which provides a specific average activity of at least 0.5 GBq/ μ mol.
45. A method according to any one of claims 1 to 44, which is partially or fully automated.
46. A [^{11}C]-radiolabelled phenothiazine or phenothiazine-like compound which is *obtained* by a method as defined in any one of claims 1 to 45.
47. A composition comprising a compound according to claim 46.
48. A composition comprising a compound according to claim 46 and a pharmaceutically acceptable carrier or excipient.
49. A method of PET imaging which employs a compound according to claim 46.
50. A method of PET imaging comprising the steps of:
- (i) preparing a [^{11}C]-radiolabelled phenothiazine or phenothiazine-like compound using a method according to any one of claims 1 to 45;
 - (ii) introducing said compound into a subject; and
 - (iii) PET imaging (e.g., a part of, the whole of) the subject.

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51. A compound according to claim 46 for use in a method of treatment of the human or animal body by therapy.

5 52. A compound according to claim 46 for use in a diagnostic or prognostic method practiced on the human or animal body.

10 53. Use of a compound according to claim 46 in the manufacture of a medicament for use in the treatment of skin cancer (e.g., melanoma) or a tauopathy (e.g., Alzheimer's disease).

15 54. Use of a compound according to claim 46 in the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in the diagnosis or prognosis of skin cancer (e.g., melanoma) or a tauopathy (e.g., Alzheimer's disease).

55. Use of:

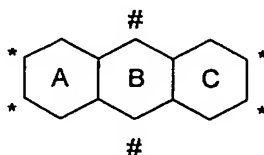
(i) a phenothiazine compound or a phenothiazine-like compound, wherein:
said compound has a polycyclic core of three six-membered rings fused together in a linear fashion and denoted the A-ring, B-ring, and C-ring, where the B-ring is the "middle" ring;

said polycyclic core is partially-aromatic or fully-aromatic;

said polycyclic core has 14 ring atoms, including exactly 1 or exactly 2 ring heteroatom(s), each of which is independently selected from N, O, and S;

the remainder of said ring atoms being C;

25 said exactly 1 or exactly 2 ring heteroatom(s) form part of the B-ring, but not part of the A-ring or C-ring, and so are located at one or both of the "central" positions denoted by a hash-mark (#) in the following depiction of the polycyclic core:



30 said compound has a pendant group covalently attached to a ring atom of said polycyclic core;

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said pendant group is independently:

- a primary amino group;
- a cationic primary imino group;
- a secondary amino group;
- a cationic secondary imino group;
- a primary imino group; or
- a secondary imino group;

and

(ii) [^{11}C]methyl trifluoromethanesulfonate ($\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$);

in the manufacture of a medicament for use in the treatment of skin cancer (e.g., melanoma) or a tauopathy (e.g., Alzheimer's disease).

56. Use of:

(i) a phenothiazine compound or a phenothiazine-like compound, wherein:

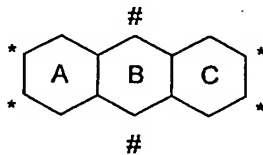
said compound has a polycyclic core of three six-membered rings fused together in a linear fashion and denoted the A-ring, B-ring, and C-ring, where the B-ring is the "middle" ring;

said polycyclic core is partially-aromatic or fully-aromatic;

said polycyclic core has 14 ring atoms, including exactly 1 or exactly 2 ring heteroatom(s), each of which is independently selected from N, O, and S;

the remainder of said ring atoms being C;

said exactly 1 or exactly 2 ring heteroatom(s) form part of the B-ring, but not part of the A-ring or C-ring, and so are located at one or both of the "central" positions denoted by a hash-mark (#) in the following depiction of the polycyclic core:



said compound has a pendant group covalently attached to a ring atom of said polycyclic core;

said pendant group is independently:

- a primary amino group;
- a cationic primary imino group;
- a secondary amino group;
- a cationic secondary imino group;

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a primary imino group; or
a secondary imino group;

and

(ii) [^{11}C]methyl trifluoromethanesulfonate ($\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$);

in the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in the diagnosis or prognosis of skin cancer (e.g., melanoma) or a tauopathy (e.g., Alzheimer's disease).

57. A method of manufacturing a medicament for use in the treatment of skin cancer (e.g., melanoma) or a tauopathy (e.g., Alzheimer's disease) which includes the steps of a method according to any one of claims 1 to 45.

58. A method of manufacturing a medicament for use in the diagnosis or prognosis (e.g., of skin cancer (e.g., melanoma) or a tauopathy (e.g., Alzheimer's disease) which includes the steps of a method according to any one of claims 1 to 45.

59. A method of treatment of skin cancer (e.g., melanoma) or a tauopathy (e.g., Alzheimer's disease) in a patient, comprising administering to said patient a therapeutically-effective amount of a compound according to claim 46.

60. A method of treatment of skin cancer (e.g., melanoma) or a tauopathy (e.g., Alzheimer's disease) in a patient, comprising the steps of:
(i) preparing a [^{11}C]-radiolabelled phenothiazine or phenothiazine-like compound using a method according to any one of claims 1 to 45;
(ii) administering to said patient a therapeutically-effective amount of said [^{11}C]-radiolabelled phenothiazine or phenothiazine-like compound.

61. A method of diagnosis or prognosis of skin cancer (e.g., melanoma) or a tauopathy (e.g., Alzheimer's disease) which employs a compound according to claim 46.

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62. A method of diagnosis or prognosis of skin cancer (e.g., melanoma) or a tauopathy (e.g., Alzheimer's disease) comprising the steps of:

(i) preparing a [^{11}C]-radiolabelled phenothiazine or phenothiazine-like compound using a method according to any one of claims 1 to 45;

(ii) introducing said [^{11}C]-radiolabelled phenothiazine or phenothiazine-like compound into the subject;

(ii) determining the presence and/or location and/or amount of [^{11}C]-radiolabelled phenothiazine or phenothiazine-like compound in (e.g., a part of, the whole of) the subject;

(iii) correlating the result of the determination made in (ii) with a disease condition of the subject.